行政院國家科學委員會專題研究計畫 成果報告

前額葉皮質對欲求類制約學習的行為功能探討((2/2)

計畫類別：個別型計畫
計畫編號：NSC 91－2413－H－004－016
執行期間：91 年 08 月 01 日 至 92 年 07 月 31 日
執行單位：國立政治大學心理學系

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報告類型：完整報告
處理方式：本計畫可公開查詢

中 華 民 國 93 年 2 月 10 日

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執行日期: 91.8.1 - 92.7.31.

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民 國 九 十 三 年 二 月 六 日

Introduction

A growing body of evidence has clearly shown the anatomical relationship between the prefrontal cortex (PFC) and mesolimbic dopamine (DA) systems. But the nature of its functional relationship or how behavioral performance may be mediated by neural pathway remains obscure. This project aimed to reveal the role of PFC on the conditioned behavior and to enhance understanding its integrity for the brain reward mechanisms. A pile of experimental evidence has shown that the function of PFC is related to either reflexive or cognitive type of behavior. In comparing to this, the data for evaluating the function on the conditioned behavior are less collected, especially for that based on appetitive learning. It is reasonable to infer that the previous known about the reward mechanisms of the mesolimbic DA systems should be relevant to the function of the PFC. One way to elucidate this issue relies on examining the function of PFC on the conditioned behavior. The present work, thus, employed two conditioned behavior tasks based on appetitive learning: the operant behavior and psychostimulant induced locomotion behavioral sensitization. Accordingly, this report covers two main studies as described in the following.

I. The role of PFC on the operant behavior

In this study, the main type of operant behavior currently used in this project was based the schedule of reinforcement called the differential reinforcement of low rate response 10 sec (DRL 10-sec). That is, a subject must 'inhibit' responding until at least 10 sec elapsed in order to obtain the reinforcer. Any response made in less than 10 sec would not be reinforced and lead to reset the 10-sec interval. Besides the basic reinforcement process is involved in the establishment of any type of operant behavior, the DRL typed behavior is characterized with behavioral inhibition and timing perception (Liao & Cheng, 2001; Sanger, 1989). The first part is concerning the lesions of mPFC on DRL 10-sec behavior in terms of acquisition and performance. The second part presents the effects of selective DA receptor antagonists on the alteration of DRL behavioral performance induced by amphetamine.

Methods

Subjects

The subjects were male Wistar rats, averaging approximately 250 g of body weight upon receipt. After 10 days of adaptation with food and water ad libitum, the rats were maintained on a water deprivation regimen such that 5 min access to tap water in the home cage occurred no sooner than 30 min after the end of each daily experimental session. The rats were monitored and kept at 85 percent of their

pre-experimental body weight. Food pellets were continuously available in each home cage. Training and/or test sessions were administered daily at the same time (10:00 to 15:00) each day during the light portion of the vivarium's 12/12 hr light-dark cycle.

Apparatus

Operant responses were measured in two chambers located in a room separate from the animal colony. Two chambers were serviced by a microcomputer. The interior dimension of each chamber was 20 cm by 25 cm by 30 cm. Aluminum panels formed the front and back walls, and clear plexiglas comprised the remaining sides and top. Stainless steel bars (diameter 5 mm) were set 11 mm apart to provide flooring. Each chamber was equipped with a lever placed 4 cm above the floor and positioned 4 cm from the right corner of the front panel. A liquid dispenser was set outside of the front of the chamber. The reinforcer (water) delivery mechanism containted 0.2 ml water for each presentation. The water was delivered into a receiving dish located on the center of the front panel and 4 cm above the floor. The chamber was illuminated by a small light bulb located 10 cm above the floor and positioned 5 cm from the left corner of the front panel. The chamber was enclosed in a plywood box with a fan to provide the necessary ventilation and masking noise. The contingency for each schedule of reinforcement was programmed and compiled via a commercial kit, Medstate Notation (MED Associate Inc., East Fairfield, VT, USA).

Procedure

In regarding the first part of this report, two experiments were conducted to determine the effects of mPFC lesion on the acquisition and maintenance of DRL 10-sec behavior, respectively. For the maintenance part, rats were initially shaped to press the lever on a continuous reinforcement schedule. Afterwards, subjects were divided into three groups and further trained to respond on a DRL 10-sec schedule for reinforcement contingency. In DRL10-sec, a reinforcer was delivered contingent upon a lever press if at least 10 sec had elapsed since the previous press. Each lever press, reinforced or not, reset the delay timer. Each daily session was 15 min in duration for all three types of operant responding. The criterion for definition of a stable baseline was less than 10% variation in the response rate under each schedule for three consecutive sessions. Following stable operant performance, each subject was conducted with the excitotoxic lesions by using ibotenic acid (5 ug/site). As determined by Paxinos and Watson (1986), the lesions were made in the ventral mPFC (AP +2.7, L ±0.7, D –5.2) and the dorsal mPFC (AP +2.7, L ±0.7, D –4.0). The AP and L coordinates were determined relative to the bregma and the depth was determined relative to the dura surface. The post-lesion test was conducted for five

days after one week of recovery from surgery. In the other experiment, naïve rats were tested for the mPFC lesions on the acquisition of DRL 10-sec behavior. The aforementioned procedures of mPFC lesions were applied before these subjects the operant learning phase. The coordinates for the subareas of mPFC were a little bit different from the preceding experiment, but still kept the contrast relativity in ventral vs. dorsal axis. The ventral site was also known as the pre-limbic/infra limbic area (PL-IL; AP +2.7, L ±0.7, D –4.6), while the dorsal site was the anterior cingulate area (AC; AP +2.7, L ±0.7, D –2.0). Three stages based on different schedules of reinforcement were assigned to acquire the DRL 10-sec behavior, which were the fixed-ratio 1 (FR1) for 5 sessions, the fixed-ratio 5 (FR5) for 5 sessions, and then the DRL 10-sec for 16 sessions.

In regarding to the second part of this report, water-deprived rats were trained to press lever on the reinforcement contingency of DRL 10-sec. The drug treatment was conducted after the subject's responding reached the baseline level. Each subject repeatedly received the systemic injection of d-amphetamine along with local infusion of DA receptor antgonist in the mPFC. The coordinates for drug infusion in the mPFC in this experiment were AP +3.7, L ±0.7, D –4.5. D-amphetamine (1 mg/kg) was injected via IP route, whereas the selective D1 and D2 receptor antagonists (SCH23390 and reclopride, respectively) were locally infused into the mPFC in the doses of 3 and 30 nmole. Both DA receptor antgonist and d-amphetamine were almost simultaneously given at 15 min before the behavioral session.

Results

Figure 1 shows the effects of (ventral and dorsal) mPFC subareas lesions on the performance of DRL 10-sec behavior. The data were presented on three pre-lesion days and five post-lesion days. Before lesion, these subjects were well trained in responding to the DRL 10-sec schedule of reinforcement. As compared to the sham controls, the excitotoxic lesions on either the ventral or the dorsal of mPFC did not significantly affect the performance of DRL 10-sec behavior. Revealed from 2-way ANOVA (2 groups by 5 post-lesion days), neither the number of total responses nor the number of reinforced responses was significantly changed by the lesion ($p>0.05$).

Figure 2 presents the effects of mPFC lesions in the PL-AL and AC areas on the acquisition of DRL 10-sec behavior. The data collected from each stage of FR1, FR5, and DRL 10-sec, were analyzed by a 2-way (group by session) ANOVA. While lack of the significant group effect, the main effects of session were significantly revealed for FR1, $F(2,76)=26.61$, FR5, $F(2,76)=7.209$, and DRL 10-sec, $F(2,285)=67.322$, all $p<0.01$. An additional ANOVA revealed that the ratio of

responses made from the last session of FR1 to the first session of FR5 was significantly different between 3 groups, $F(19)=4.099$, $p<0.05$. Post-test comparisons indicated the difference between the AC lesion and sham control was significant ($p<0.05$). In addition to analyzing the gross responding by scrutinizing the number of total responses, further analyses were made on the inter-response times (IRT) distribution for the DRL 10-sec. Figure 3 shows the effects of mPFC lesions on the IRT distribution (by every 1 sec bin) over the 1st, the 9th, and the 16th session of the DRL 10-sec stage. The lesion effects mainly appeared on the first two bins in which responding was so-called burst response. Although all three groups gradually gained the reinforced responses over the acquisition stage in about the same degree, the AC lesion group produced a higher number of burst responses at the 9th and the 16th session in comparing to the other two groups.

The effects of selective DA D1 and D2 receptor antagonists on the alteration of DRL 10-sec behavior induced by d-amphetamine are shown in the Figure 4 and Figure 5, SCH23390 and raclopride, respectively. From these two figures, d-amphetamine given alone significantly increased the total responses and decreased the reinforcers earned. Surprisingly, the burst responses of DRL behavior increased by d-amphetamine alone were not significant in statistics. The peak time of the inter-response times distribution was significantly decreased by d-amphetamine, which effects are also presented in the leftward shift of distribution curves of d-amphetamine from the controls. Thus, these data present the apparent alteration of DRL behavioral performance induced by systemic d-amphetamine. Either SCH23390 or raclopride reversed the gross deficits, on the responses and the number of reinforcers earned, of DRL responding induced by d-amphetamine. However, SCH23390, but not raclopride, at the higher dose reversed the peak time shortened by d-amphetamine.

Discussion

The results from the first part of this study show that the mPFC is involved in the acquisition, but not the performance, of DRL 10-sec behavior. The different effects resulted from excitotoxic lesions in the PL-AL and the AC areas of mPFC confirm the heterogeneous functions within the mPFC subareas for the rat in operant conditioning based on the DRL schedule of reinforcement. The AC area of mPFC was found to be important in the establishment of DRL 10-sec behavior by observing the difficulty in shifting the burst responses to the reinforced responses (see figure 3). Based on the water as the reinforcer applied the present work, the operant behavior can be characterized as the appetitive-conditioning paradigm. The mPFC lesions impaired the establishment of DRL 10-sec behavior. Thus, the mPFC must be involved in the

behavior conditioned via appetitive-conditioning process, which is a main concern of this proposed study. However, more data are needed to evaluate this proposed issue in the systematic manner.

In addition to appetitive-conditioning, the timing process involved in the mPFC for DRL behavior is concerned by this study. These data shown in the Figure 4 and Figure 5 confirm that d-amphetamine can disrupt the timing regulation of DRL behavior by increasing the internal 'clock' speed. Furthermore, blockade of dopamine D1 receptors in the mPFC are involved in reversing such behavior alteration. This part of findings is compatible to a most recent argument proposing that the temporal processing occurs in the PFC (Lewis, 2002), which evidence was supported by finding delays in cell activity within milliseconds produced by pairs of dorsomedial prefrontal neurons (Constantinidis et al., 2002).

II. The role of PFC on the psychostimulant induced locomotion behavioral sensitization

Behavioral sensitization to psychostimulant drugs is now a well-known phenomenon, wherein animals show enhanced behavioral reactivity after repeated drug exposure (Robinson & Becker, 1986). Attention has focused the critical role of the mesotelencephalic dopamine (DA) systems on amphetamine- or cocaine-induced sensitization on several types of behavioral measurements including locomotor activity (Kalivas & Steward, 1991; Pierce & Kalivas, 1997; Robinson & Berridge, 1993). Specifically, dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens are critically involved in the induction and expression of behavioral sensitization to psychostimulant drugs (e.g. Cador et al., 1995; Kalivas & Weber, 1988).

In addition to the mesolimbic DA systems, it is reasonable to refer the involvement of the mesocotical DA systems in this type of behavioral sensitization. The mPFC has been known as a major terminal area with DA afferent inputs from the VTA (Thierry et al., 1990). Recently, accumulating data suggest that the functional role of mPFC on the reward-related behavior is highly linked to drug effects of psychostimulants (for review see Tzschentke, 2001). Several studies reported that lesions of mPFC attenuate the induction of behavioral sensitization to cocaine (Tzschentke & Schmidt, 1998 & 2000) and amphetamine (Cador et al., 1999; Wolf et al., 1995). Once established, the expression of behavioral sensitization to cocaine was suppressed by mPFC lesions (Pierce et al., 1998). However, negative results for mPFC lesion on behavioral sensitization to either psychostimulants were also reported (Li et al., 1999; Li & wolf, 1997; Tzschentke & Schmidt, 2000). These controversial

data may derive from the different sizes and locations in the mPFC produced by lesions applied in those studies. Another factor leading this controversy is due to different protocols to induce psychostimulant sensitization being applied. Especially, the environmental contexts where conducting the repeated drug administrations were differentially adopted by those studies. The magnitudes of behavioral sensitization to psychostimulants can be different when distinct environments to conduct repeated drug administrations being manipulated (Robinson et al., 1998). Thus, it is possible that this controversy is due to these two confounding factors.

The present study intended to further contend with this issue by investigating the effects of excitotoxic lesions in two subareas of mPFC on the development of behavioral sensitization to d-amphetamine in different environments. In the first part of experiment, we established three protocols for d-amphetamine induced locomotion sensitization by manipulating the repeated intermittent drug administrations in three distinct environments including 1) the test box, 2) the home cage, and 3) a novel third place. Due to the least effectiveness of d-amphetamine to induce locomotor sensitization in the novel third place, the second part of experiment examine the effects of lesions in the dorsal and ventral subareas of mPFC on the development of locomotor sensitization to d-amphetamine in the test box and home cage.

Methods

Subjects & Surgery

The subjects used in this study and the lesion work with stereotaxic surgery were similar to those described in the preceding study.

Apparatus

The locomotor activity was measured by an infrared motion sensor activity system (Coulbourn Instruments). Consisting of paired pryoelectric detectors, each infrared motion sensor, attached to the top of a white plastic box (50 x 25 x 30 cm), measured the radiated body heat of the subject's motion. A bank of 6 boxes, as served by a microcomputer, was used in this study. The sensor's output signal representing magnitude of the subject's spatial movement was digitally converted and stored for data analysis. Each motion continuously lasting 1 sec or longer was defined as a movement and counted, which duration was also accumulated. The activity boxes were set in a separate room with dimly lit and constant background noise.

Procedures

The experiment consisted of three stages in the following sequence 1) pre-test, 2) repeated exposure of drug, and 3) post-test for sensitization. In the pre-test stage of

four-day period, all subjects were placed in the locomotor activity test box for 2.5 hr on the first and fourth days. As the first 30 min elapsed when staying in the test box, the subject was given an injection of saline on the first day and an injection of a lower dose d-amphetamine (0.5 mg/kg) on the fourth day. The locomotor activities measured on the fourth day were taken as the pre-test data. The stage of repeated exposure of drug was began one week after the completion of the pre-test stage. The subject was repeated injected with d-amphetamine of 1.0 mg/kg for seven times in every other day. There were three distinctive environments to conduct this repeated exposure of drug including the test box, the home cage, and a novel third place. For the subjects injected in the test box, they were placed in the locomotor activity box for 30 min and then given with drug injection. Following this injection, they were remained staying in the box for another 2 hr. For the subjects injected in the home cage, they were given the drug injection in their own home cages at about the same time period of the daily session as the subjects in other two groups. For the subjects injected in the third place, they was removed from colony room to a separate room and then placed into a novel Plexiglas box for 2.5 hr. During which, they were given the drug injection as the first 30 min elapsed and remained staying for the rest 2 hr. Subsequently, they returned to their home cages in the colony room. In order to compare the specific effect of drug administration paring to the test box or home cage, two saline control groups were designed to receiving repeated injections of saline vehicle during this stage. Except for the injection solution, the procedures for these two saline control groups were identical to those aforementioned of repeated drug exposure in the test box and home cage. The stage of post-test of locomotor sensitization was conducted two days after the end of repeated drug exposure as described above. All subjects were treated with the same procedures described for the fourth day of the pre-test stage. Behavioral sensitization to d-amphetamine was judged by the significant enhancement of locomotor activity in the post-test by comparing those data from the pre-test within each group. There were five groups (n = 8 each) in total for the first part of experiment.

Two cohorts of subjects with excitotoxic lesions in the dorsal and ventral subareas of mPFC were used for the second part of experiment. The subjects with lesion of each mPFC subarea were further divided into two subgroups for receiving the repeated exposure of d-amphetamine in the test-box and home cage, respectively, which procedures were the same as those described above. In addition to these four lesion groups, there were four sham lesion groups served as the contols. Following the completion of behavioral testing, histological examination of the lesion area was conducted for each subject.

Results

Fig. 6 shows the results of the first part of experiment in depicting the development of locomotor sensitization to d-amphetamine in three distinct environments. Data regarding the number of movement counts are presented in the top panel of Fig. 6. As revealed from the results of a 2 by 2 ANOVA for the test-box treatment, there was only a significant main effect for pre- and post-test, $F(1, 14) = 13.86$, $p < 0.01$. Neither the group main effect nor the interaction was significant. Planed comparisons showed a significant increase of locomotor activity in the post-test for the d-amphetamine treated group, $F(1, 14) = 14.48$, $p < 0.01$. The ANOVA results for the home cage were similar to those of test-box. That is, only a significant main effect for pre- and post-test was detected, $F(1, 14) = 7.48$, $p < 0.05$. And, a significant increase of locomotor activity in the post-test for the d-amphetamine treated group was yielded from planed comparisons, $F(1, 14) = 6.2$, $p < 0.05$. Regarding the group receiving the repeated exposure of d-amphetamine in the third place, the increased movement counts in the post-test did not reach the significant level, $F(1, 7) = 4.5$, $p = 0.069$. The bottom panel of Fig. 6 presents data regarding the accumulated duration of movements. As revealed from the results of a 2 by 2 ANOVA for the test-box treatment, both tests of main effect were significant: $F(1, 14) = 4.66$ for drug exposure and $F(1, 14) = 11.05$ for the pre- and post-test (both $p < 0.05$). The interaction of drug exposure and test stage was not significant. Planed comparisons showed a significant longer duration accumulated in the post-test for the d-amphetamine treated group, $F(1, 14) = 13.24$, $p < 0.01$. The 2 by 2 ANOVA conducted for the duration data for home cage treatment did not yield any significant result for main effect or interaction test. Regarding the group receiving the repeated exposure of d-amphetamine in the third place, the duration of movements was significantly longer in the post-test that in the pre-test, $F(1, 7) = 6.14$, $p < 0.05$. A separate 3 by 2 ANOVA was conducted to compare the differences existing three groups receiving repeated exposure of d-amphetamine conducted in three distinctive environments. Only the main effect of test stage was significant, $F(1, 21) = 23.66$ for the number of movements and $F(1, 21) = 22.16$ for the duration of movements (both $p < 0.001$). Neither the group main effect nor the interaction was significant. Planed comparisons further showed significant differences on the duration variable when comparing the groups receiving repeated drug exposure in the test-box and home cage, $F(1, 21) = 6.35$, and comparing those groups in the test-box and the third place, $F(1, 21) = 5.28$ (both $p < 0.05$).

Fig. 7 shows the results of histological examination in the second part of experiment. Lesions of the dorsal mPFC were mainly located in area Cg1, extending about 1 mm vertically from dura without destructing the infralimbic area. Lesions of

the ventral mPFC were mainly located the infralimbic area and the bottom half of area Cg3, which did not extended to area Cg1. The rostrocaudal extent of these two lesions approximately located from 4.0 mm to 2.0 mm anterior to bregma.

Fig. 8 shows the effects of lesions in mPFC subareas on the development of locomotor sensitization to d-amphetamine in the test-box and home cage. As shown in the top panel of Fig. 8, a 2 by 2 by 2 ANOVA conducted on the number of movements only detected the main effect of test stage, $F(1, 24) = 16.67$, $p < 0.001$. None of the other two main effects and interaction tests were significant. Planed comparisons yielded significant differences between pre- and post-test for all treatment groups ($p < 0.05$) except the ventral mPFC lesion group in the test box. This pattern of statistical results showing the inhibitory effects on the induction of locomotor sensitization to d-amphetamine in the ventral mPFC lesion group is also true for the duration data as shown in the bottom panel of Fig. 8.

Discussion

The present investigated the effects of excitotoxic lesions in the dorsal and ventral subareas of mPFC on the development of behavioral sensitization to d-amphetamine in different environments. The results showed that the most profound locomotor senisitization to AMP appeared in the subjects receiving the repeated intermittent drug administrations in the test box group. A less, but significant, degree of locomotor sensitization to AMP was observed for the home cage group, which effects was significantly detected on a variable of the number of movement counts. Although a trend of locomotor sensitization to AMP observed in the third place group, it was not statistically confirmed. The results from the second part of experiment showed that locomotor sensitization was reliably appeared in any of the sham lesion control groups in either test box and home cage environment. Lesions of ventral mPFC significantly inhibited the development of behavioral sensitization to AMP in test box, but not the one in the home cage. Lesions of dorsal mPFC failed to prevent locomotor sensitization developed from either test box or home cage.

Different degrees of locomotor sensitization to d-amphetamine were measured from the subjects receiving the repeated intermittent drug injections in three distinct environments. The magnitude of locomotor sensitization to d-amphetmine developed in the test box is the highest among the three environments being tested inn the present study. The degree of locomotor sensitization to d-amphetamine in the home cage is less than that measured in the test box. The difference between these two types of locomotor sensitization may be attributed to that the association or pairing effects of drug reaction and environmental context are different for the

subjects in these two treatments. The subjects form the test box group certainly had more experience of linking drug reaction and environmental context. It has been well recognized that the environmental setting for drugs being administered can powerfully modulate the behavioral effects of drugs (Robinson et al., 1998). Using the rotation behavior induced by d-amphetamine in the unilateral 6-hydroxydopamine lesion rat, Robinson and associates reported that amphetamine produce a robust sensitization when given with placement into the test environment but not in the animal's home cage (Badiani et al., 1995; Crombag et al., 2000). This also true for locomotor sensitization developed by daily cocaine injections and then challenged by intra-accumbens infusion of glutamatergic receptor agonist AMPA, when both agents given all in the same test box (Bell & Kalivas, 1996). Moreover, using the rotation behaviroal paradigm, Anagnostaras and Robinson (1996) reported that the subjects receiving the repeated amphetamine exposure in a third world rather than the test environment and the home cage failed to produce the sensitization effect to a subsequent amphetamine challenge. Together, current data and those from other's consistently support the notion that contextural control is essentially critical for psychostimulants induced behavioral sensitization.

The results from the second part of experiment in the present study are generally congruent with those previous studies showing the disruption of behavioral sensitization to psychostimulants following mPFC lesions (Cador et al., 1999; Pierce et al., 1998; Tzschentke & Schmidt, 1998 & 2000; Wolf et al., 1995). Of a particular interest to investigate the potentially heterogeneous function of mPFC subareas on amphetamine sensitization, the present study found that the development of locomotor sensitization to d-amphetamine was inhibited after the excitotoxic lesions conducted in the ventral part of mPFC rather than the dorsal part. And, this blocking effect was only true for the locomotor sensitization to d-apetamine developed in the subjects of test-box group. In contrast to locomotor sensitization in the test-box, those developed in the home cage were invulnerable to the lesions of mPFC made in either subarea. Thus, the ventral part of mPFC is involved in the development of locomotor sensitization to d-amphetamine when the repeated drug administrations conducted in the test box all the way from pre-test to post- test stage. Given a behavioral characteristic inferring more association experience involved in the sensitization of the test box group as described above, the function of the ventral mPFC is likely to exert this hypothetical process when drug reaction interacts with the consistent surrounding environment during the development of this type of sensitization. We assume that processing the locomotor sensitization to d-amphetamine in the test box is more complex than that in the home cage. In fact, the general function of mPFC is thought to execute more complex behavioral process

(Uylings et al., 2000).

Although the mPFC lesions were shown to disrupt the development of locomotor sensitization to amphetamine, several earlier studies examined the lesion effects by damaging the whole mPFC, instead of comparing the lesion effects by destructing the mPFC subareas (Cader et al., 1999; Wolf et al., 1995). Accordingly, the present study further conducted the excitotoxic lesions in the dorsal and ventral subareas in the mPFC to address this issue. And, it was found that the ventral mPFC lesions significantly inhibit the establishment of locomotor sensitization to d-amphetamine given in the test box environment rather than in the home cage. Recently, a series of studies conducted by Tzschentke and Schmidt (1998, 1999, & 2000) to examine the lesions of three subareas (anterior cingulate, pre-limbic, and infra-limbic) in the mPFC on behavioral sensitizations to cocaine and d-amphetamine. According to their reports, cocaine induced sensitization was attenuated by lesions of the whole mPFC or pre-limbic subarea, whereas it was not affected by the lesions of anterior cingulate and infralimbic areas. In contrast to the cocaine sensitization, the development of amphetamine sensitization in their protocol was not significantly attenuated by the lesions in any of those three subareas in mPFC. Despite different protocols used to form psychostimulants-induced sensitization, it is likely that specific subareas are differentially involved in behavioral sensitizations to cocaine and d-amphetamine. In other words, the dorsal (pre-limbic) part of mPFC is for cocaine's, while the ventral part of mPFC is for d-amphetamine's as revealed from the present findings. Accumulating data support the idea that the neurobehavioral mechanisms for cocaine and d-amphetamine on reward-related or behavioral sensitization are distinctive (reviews see Pierce & Kalivas, 1997; Vanderschuren & Kalivas, 2000; White & Kalivas, 1998).

Conclusions

This project characterized the role of PFC (especially the mPFC area) on the conditioned behavior, which data enhance our understanding the integrity for the brain reward mechanisms. Data from the first study of this report indicate that the PFC is involved in mediating the appetitive-conditioning and timing process for the DRL operant behavior paradigm. From the second study, it is indicated that the heterogeneous functions of mPFC subareas involved in the development of behavioral sensitization to d-amphetamine are dependent on different contexts applied for chronic psychostimulant drug administration. Together, these data are ery informative. Some of the aforementioned data have presented or submitted in abstracts for conference meeting (Cheng & Liao, 2001; Liao & Cheng, 2002) and are currently prepared for full paper publication.

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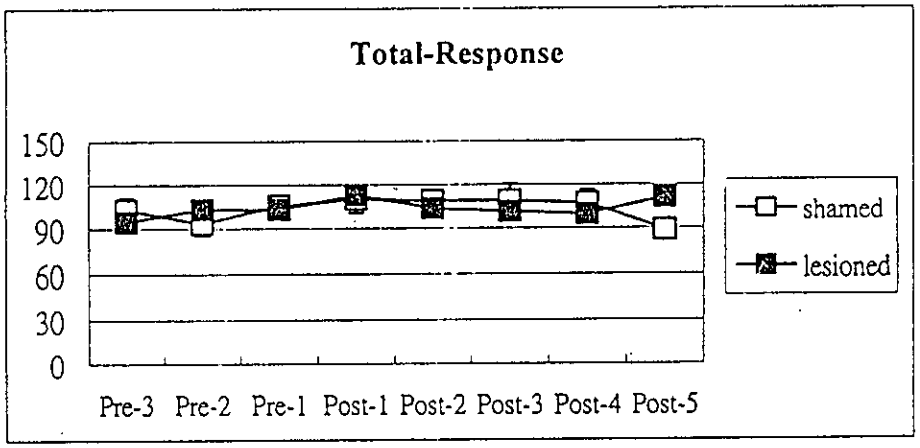
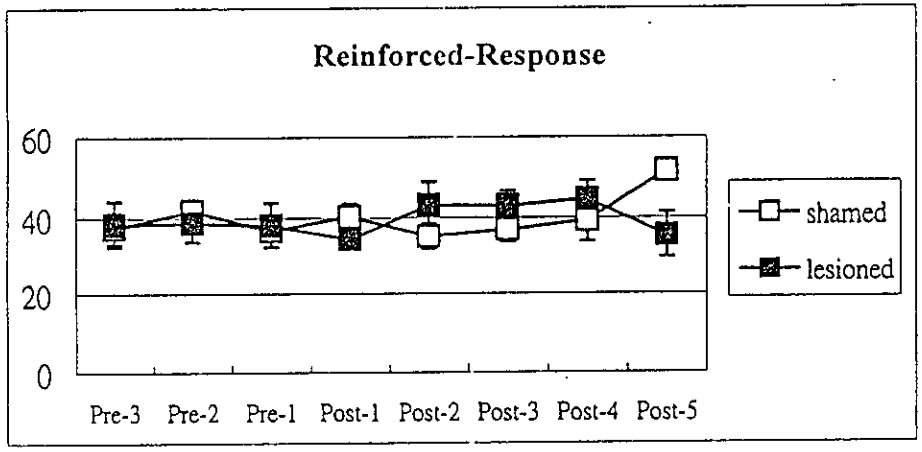
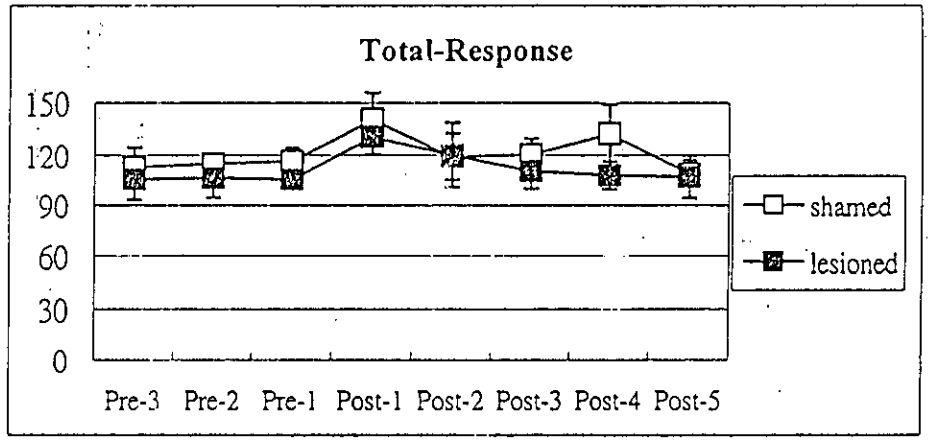
ventral mPFC lesion





dorsal mPFC lesion



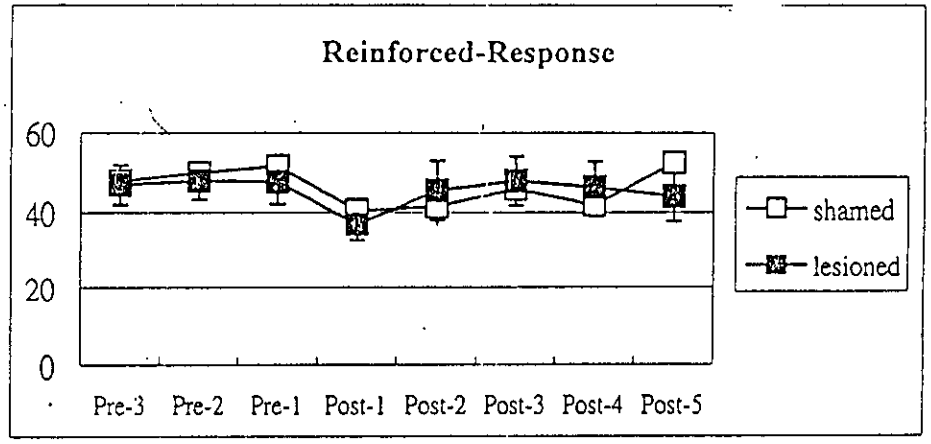


Figure 1: The effects of ventral (left 2 panels) and dorsal (right 2 panels) mPFC lesion on the performance of DRL 10-sec behavior. Data are presented as the mean ± 1 s.e.m. of the numbers of total responses and reinforced responses over three pre-lesion and five post-lesion sessions.

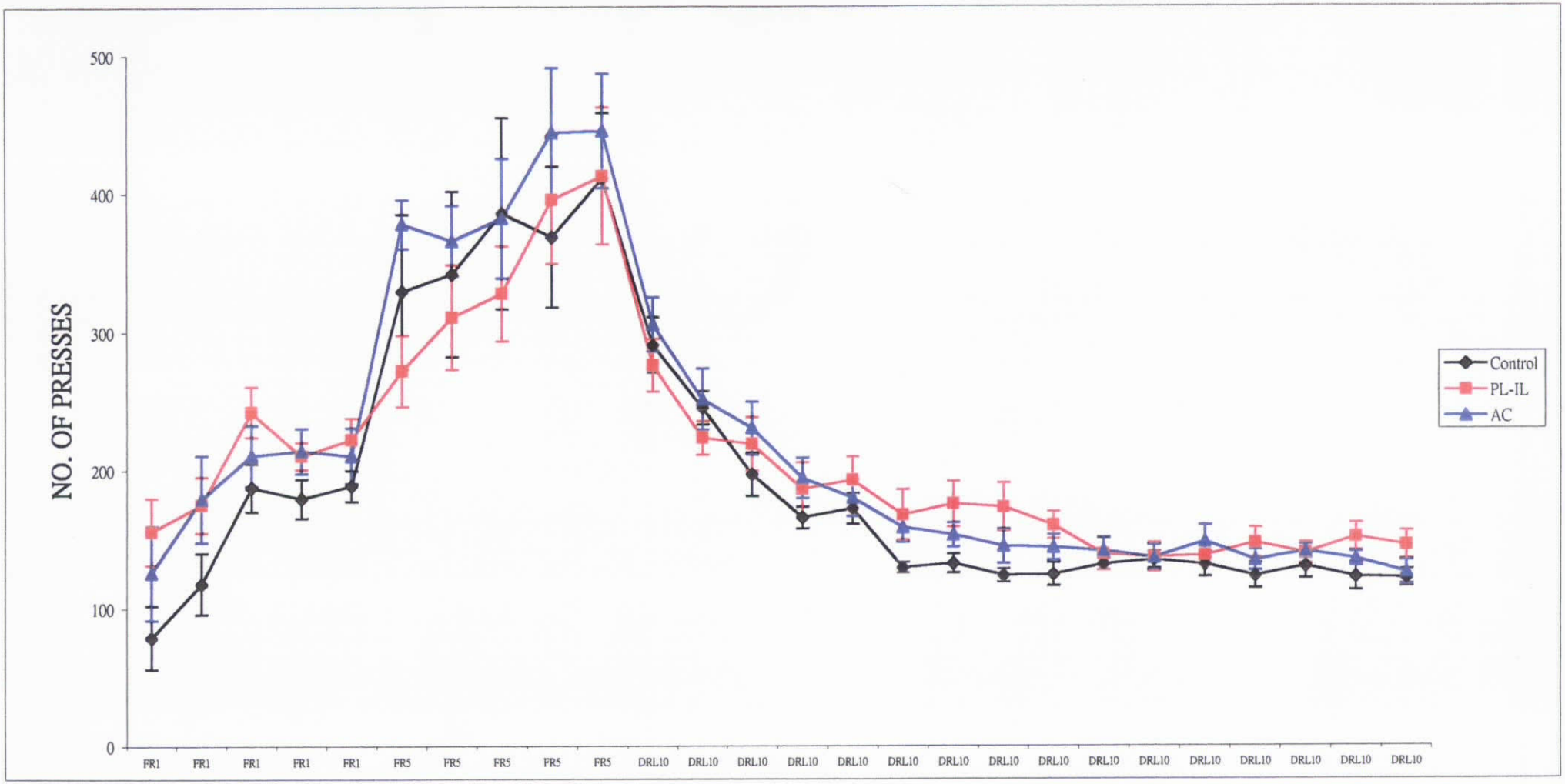
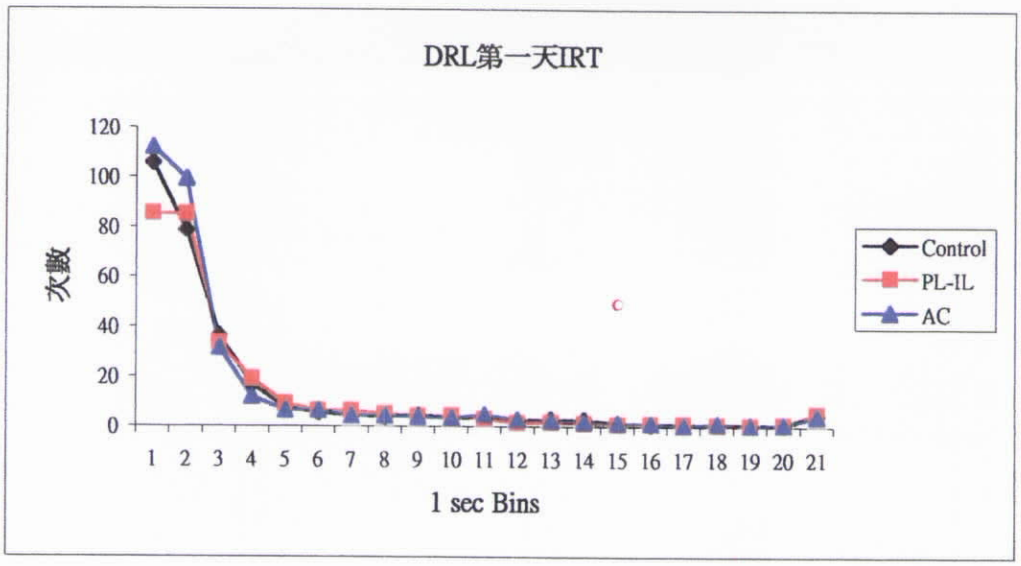
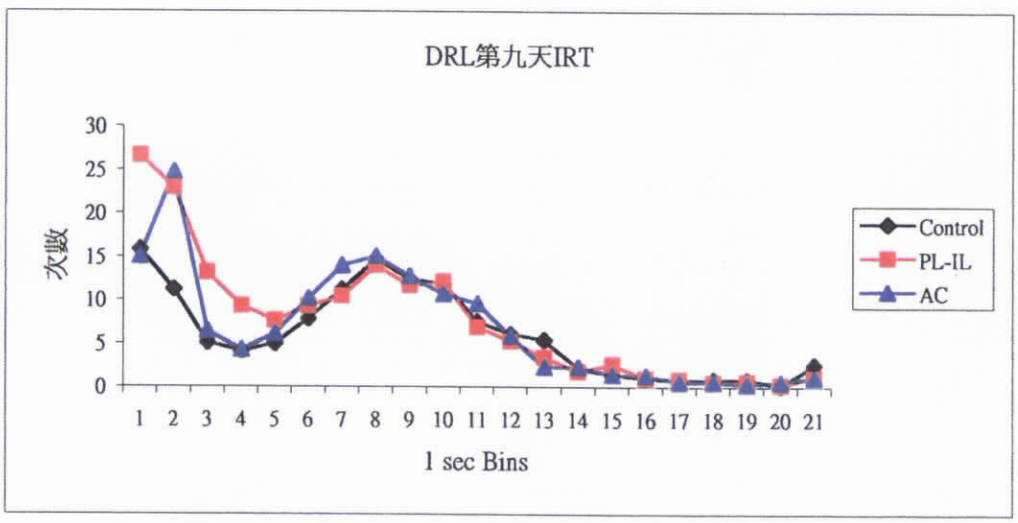


Figure 2: The lesion effects of pre-limbic/infra-limbic area (PL-IL) and anterial cingulate area (AC) of mPFC on the acquisition of DRL 10-sec behavior which operant responding was transferred from the fixed-ratio 1 (FR1) and the fixed-ratio 5 (FR5) schedule of reinforcement. Data are represented by the mean ± 1 s.e.m.





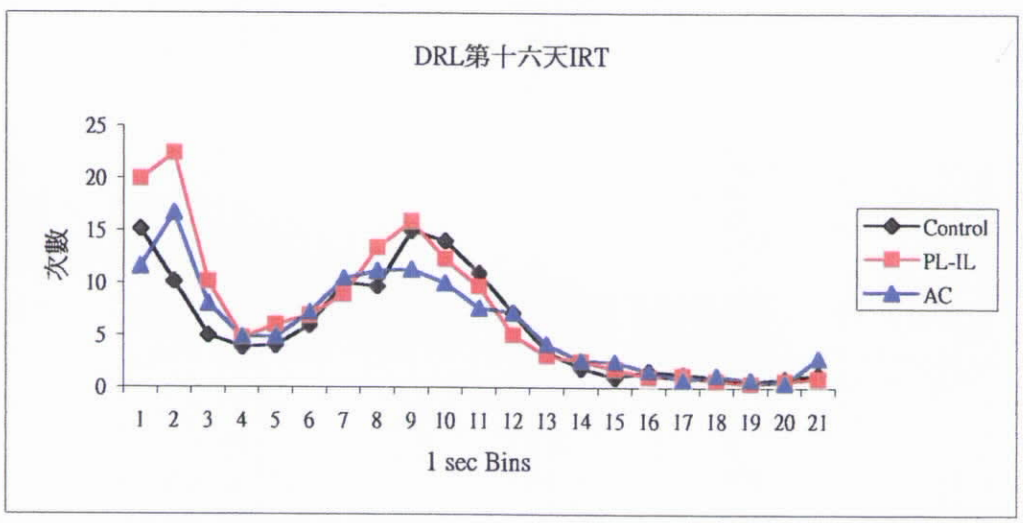
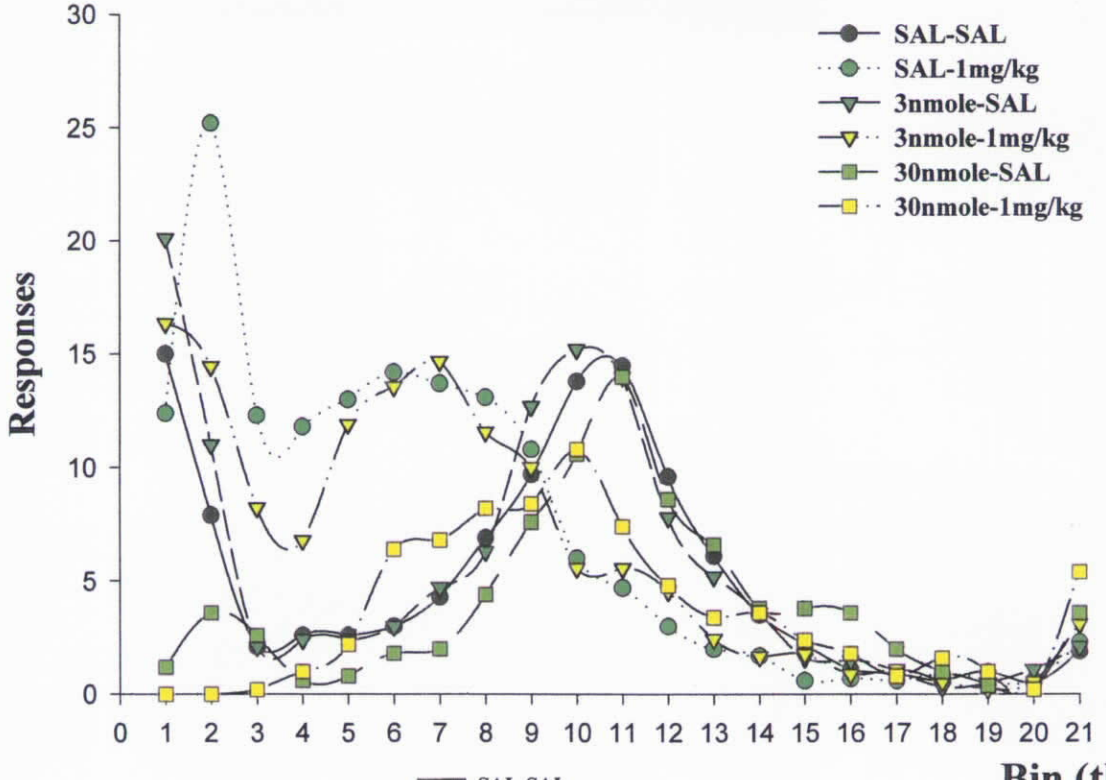
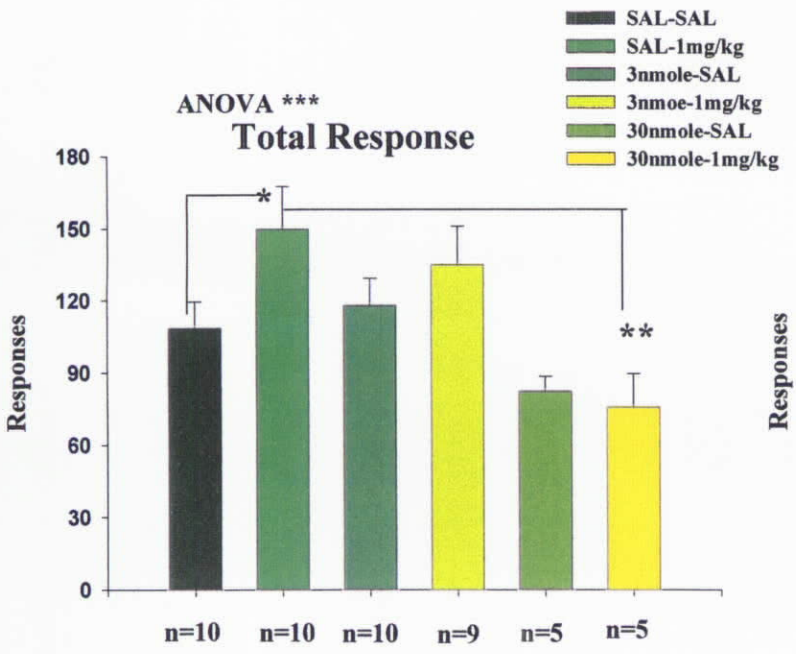


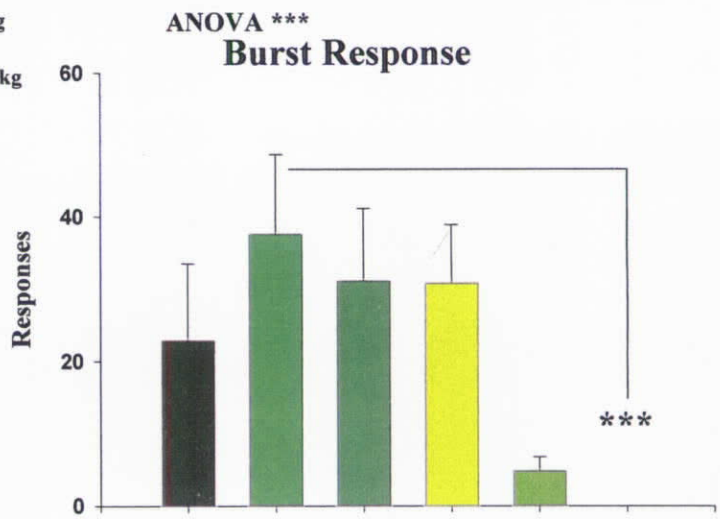
Figure 3: The lesion effects of pre-limbic/infra-limbic area (PL-IL) and anterial cingulate area (AC) of mPFC on the frequencies of inter-response times (IRT) at the 1st, the 9th, and the 16th session of DRL 10-sec behavior.

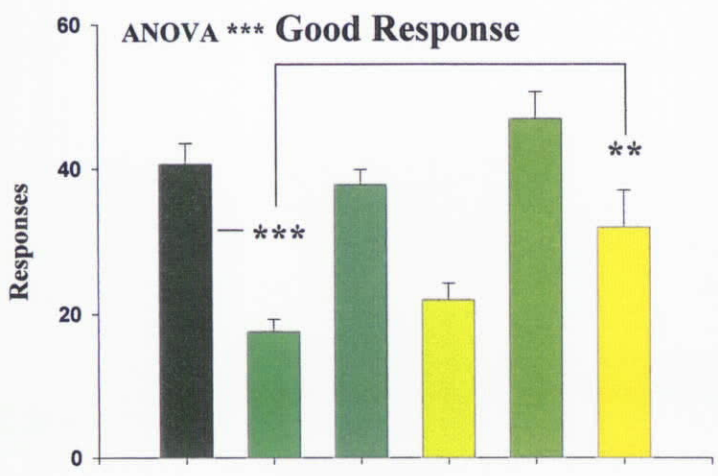
Fig. 4

SCH23390 in mPFC









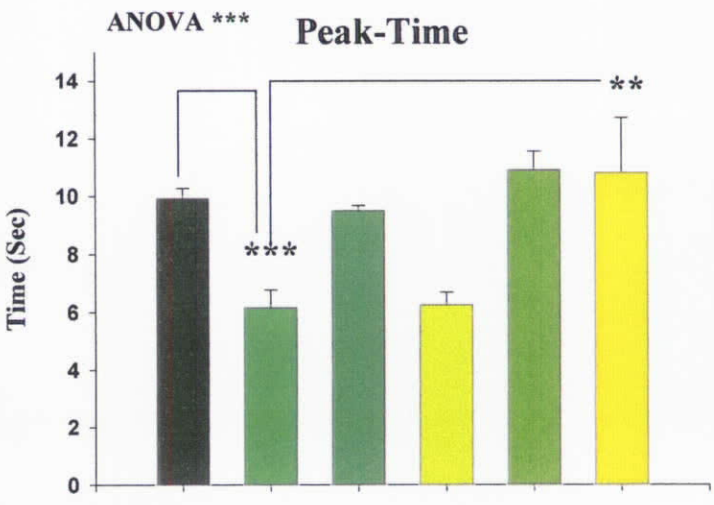
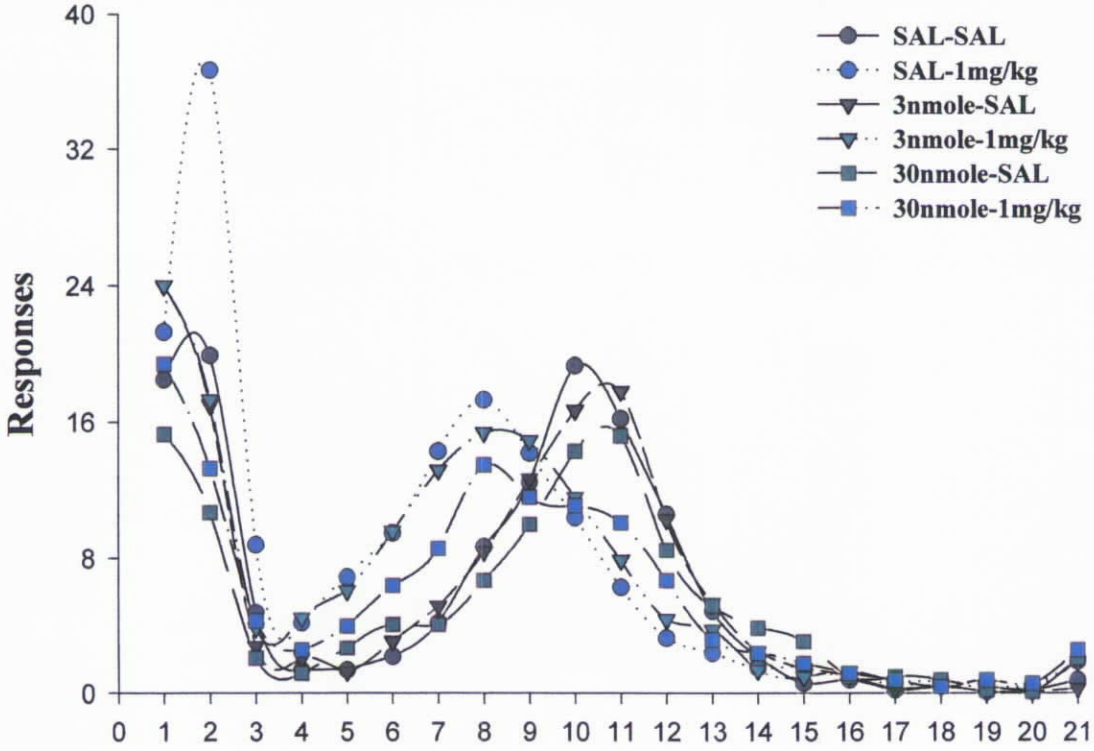
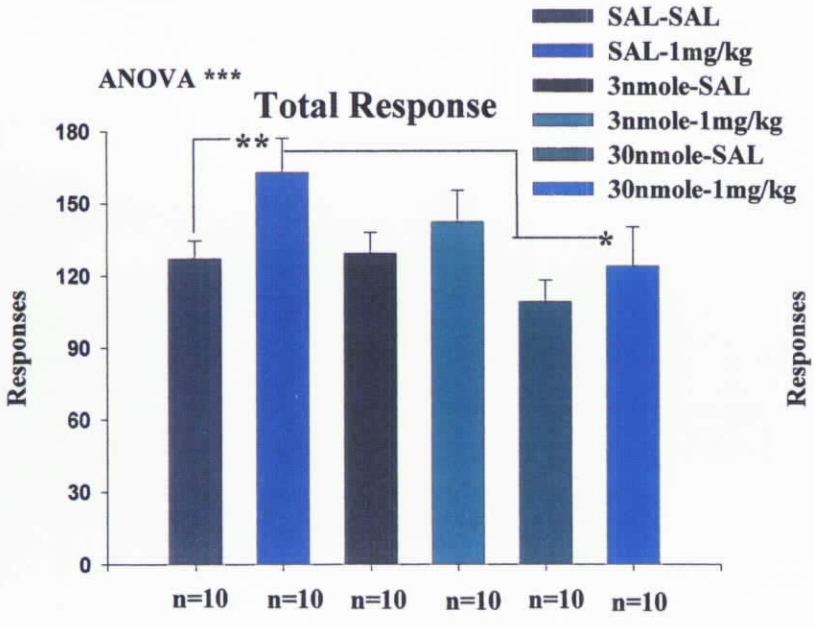
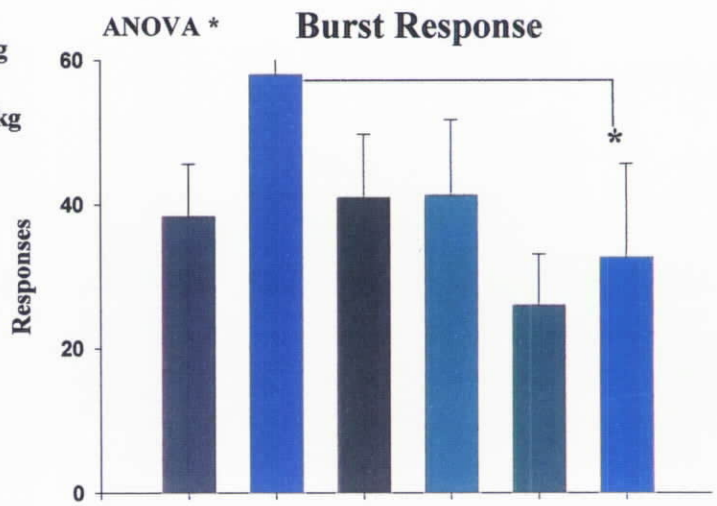


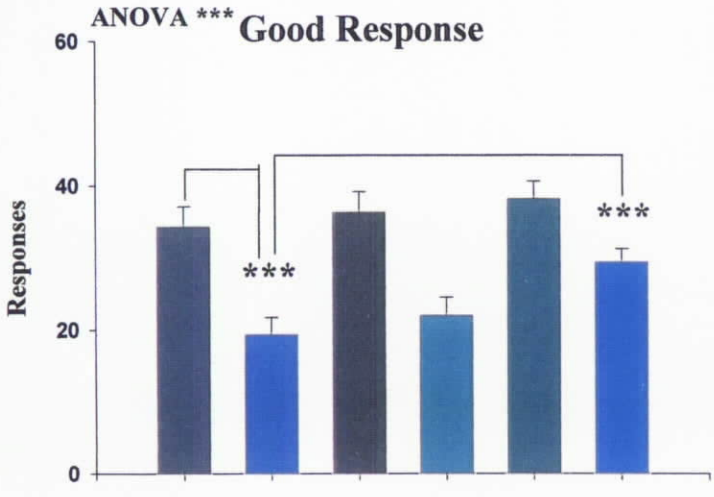
Fig. 5

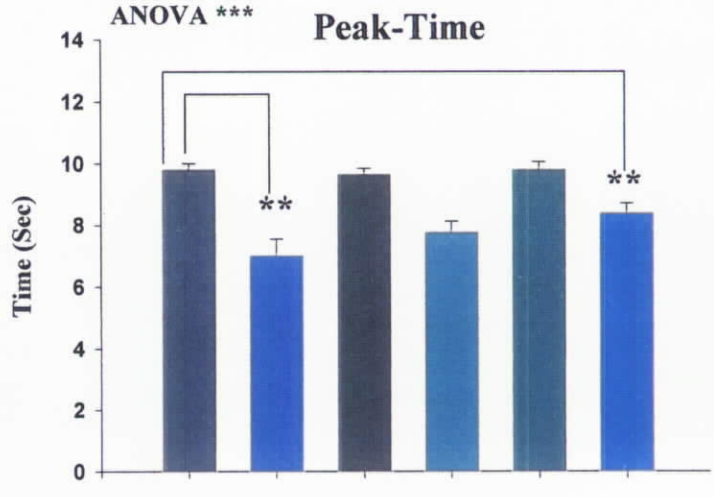
raclopride in mPFC











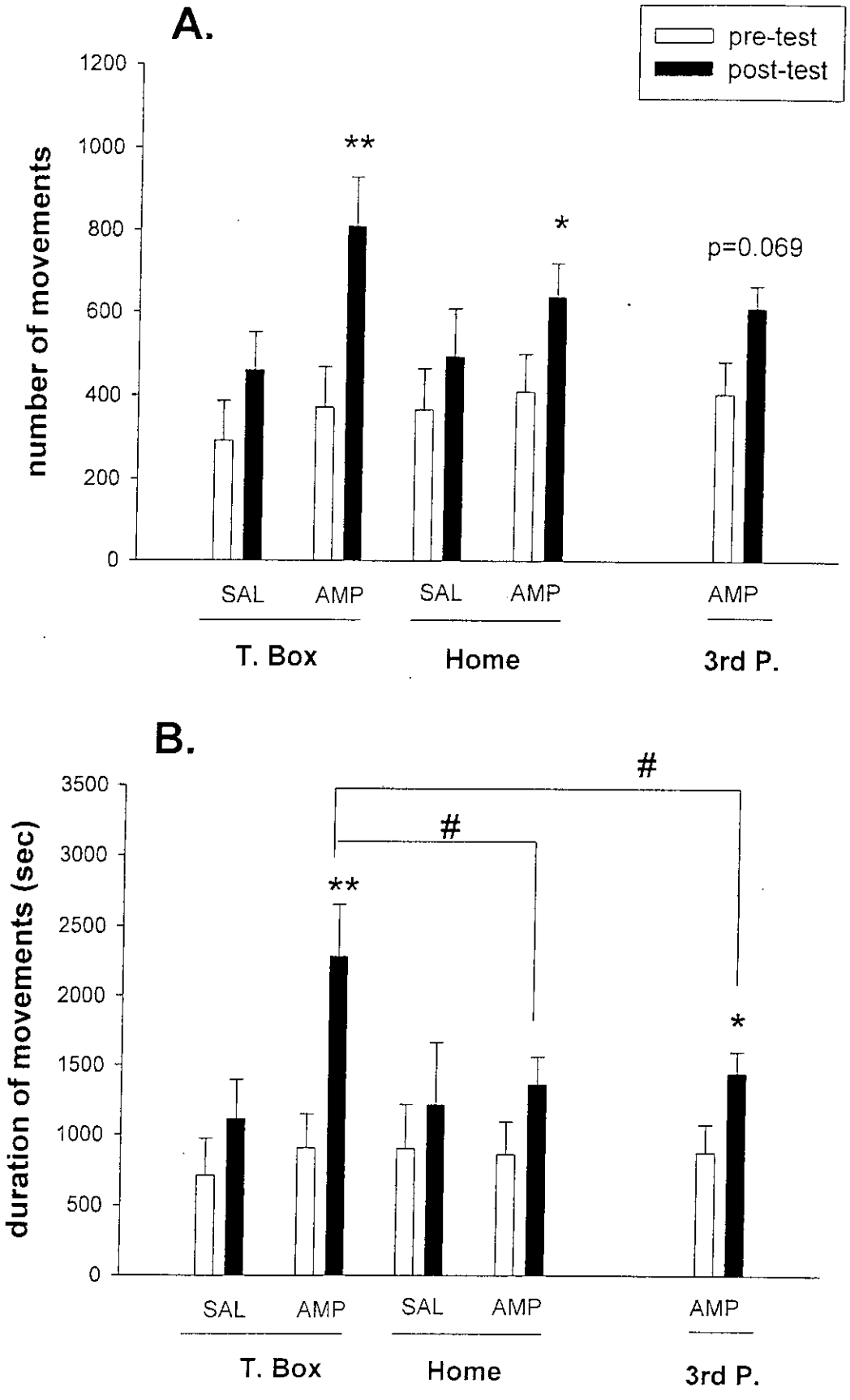


Fig. 6 Locomotor activities as measured by the number of counts (A) and the accumulated duration (B) of the detected movements on the pre- and post-test sessions for three groups of rats received d-amphetamine (AMP) repeatedly in the test box (T. box), homecage (Home), and a novel third place (3rd P.). Two saline (SAL) control groups received repeatedly injections of saline vehicle in the test-box and home cage. n = 8 for each group. Data are presented as means ±1 s.e.m. * $p < 0.05$, ** $p < 0.01$; significant difference between pre-test and post-test on the indicated group. # indicates that the significant difference between the two bars as indicate.

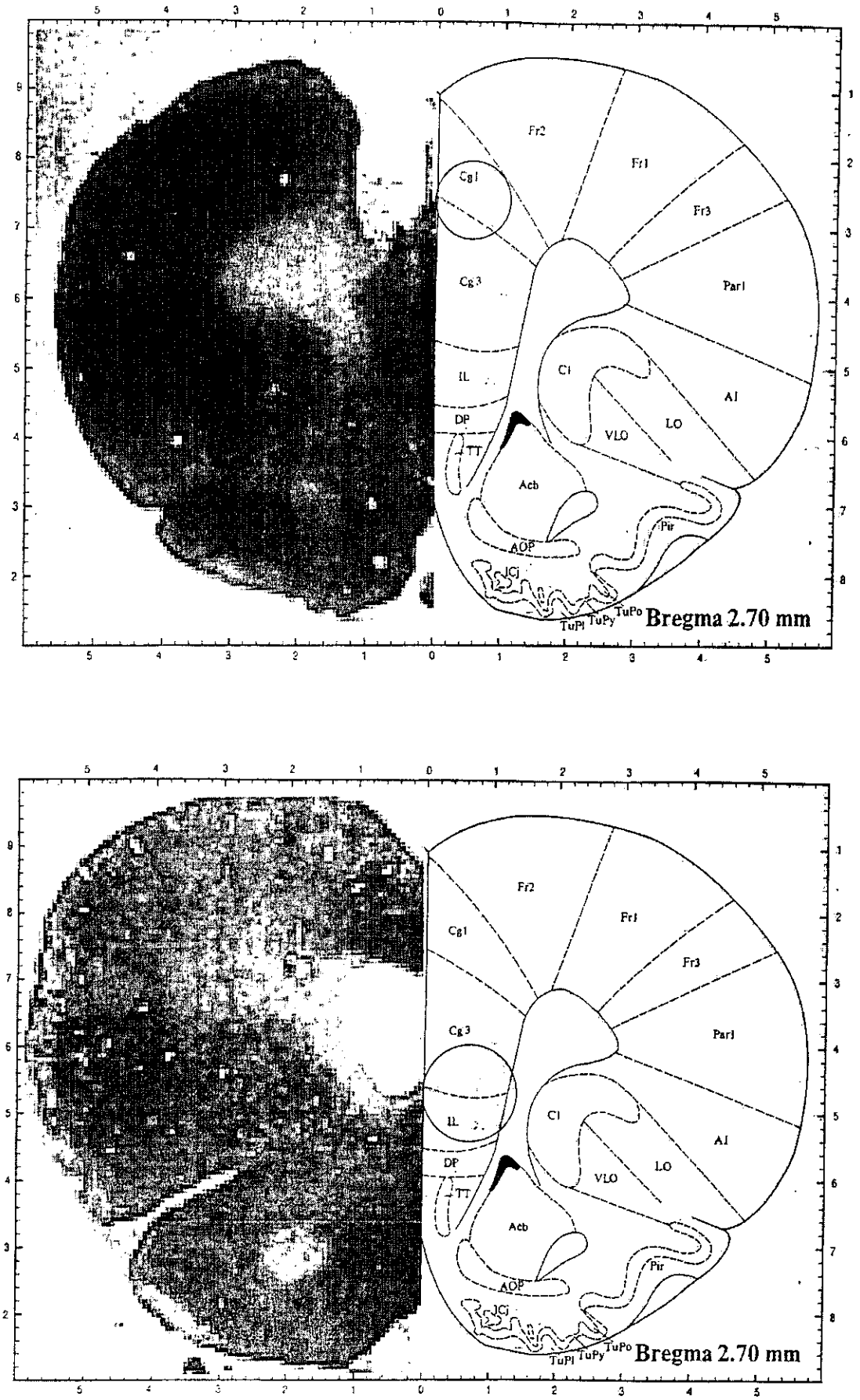
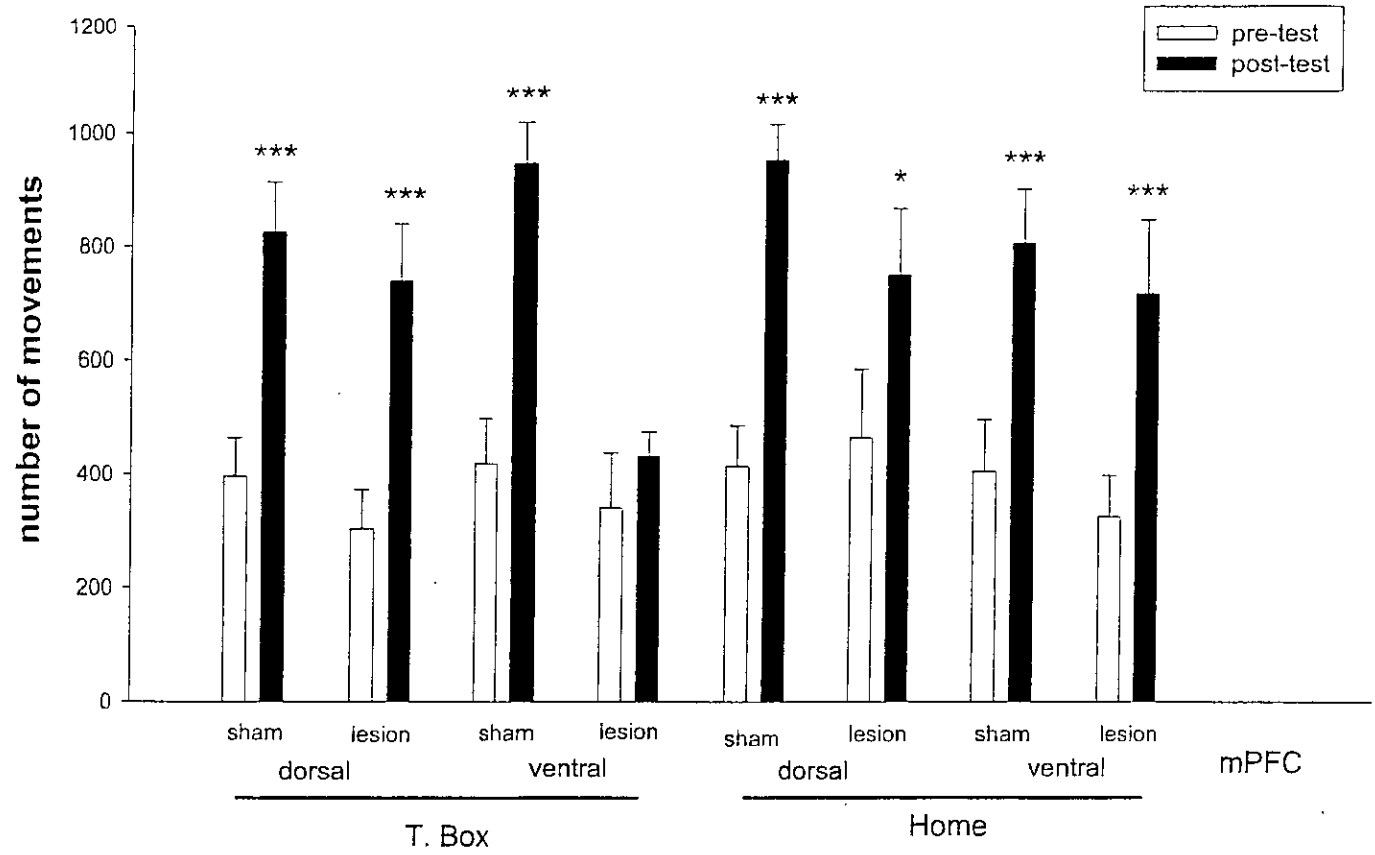


Fig. 7 Photomicrographs of ibotenic acid lesions of the dorsal (*top*) and ventral (*bottom*) subareas of the medial prefrontal cortex. Schematic diagrams, on the right side of each panel, show the largest lesions in the gray circles. Drawings were adapted from Paxinos and Watson (1986).



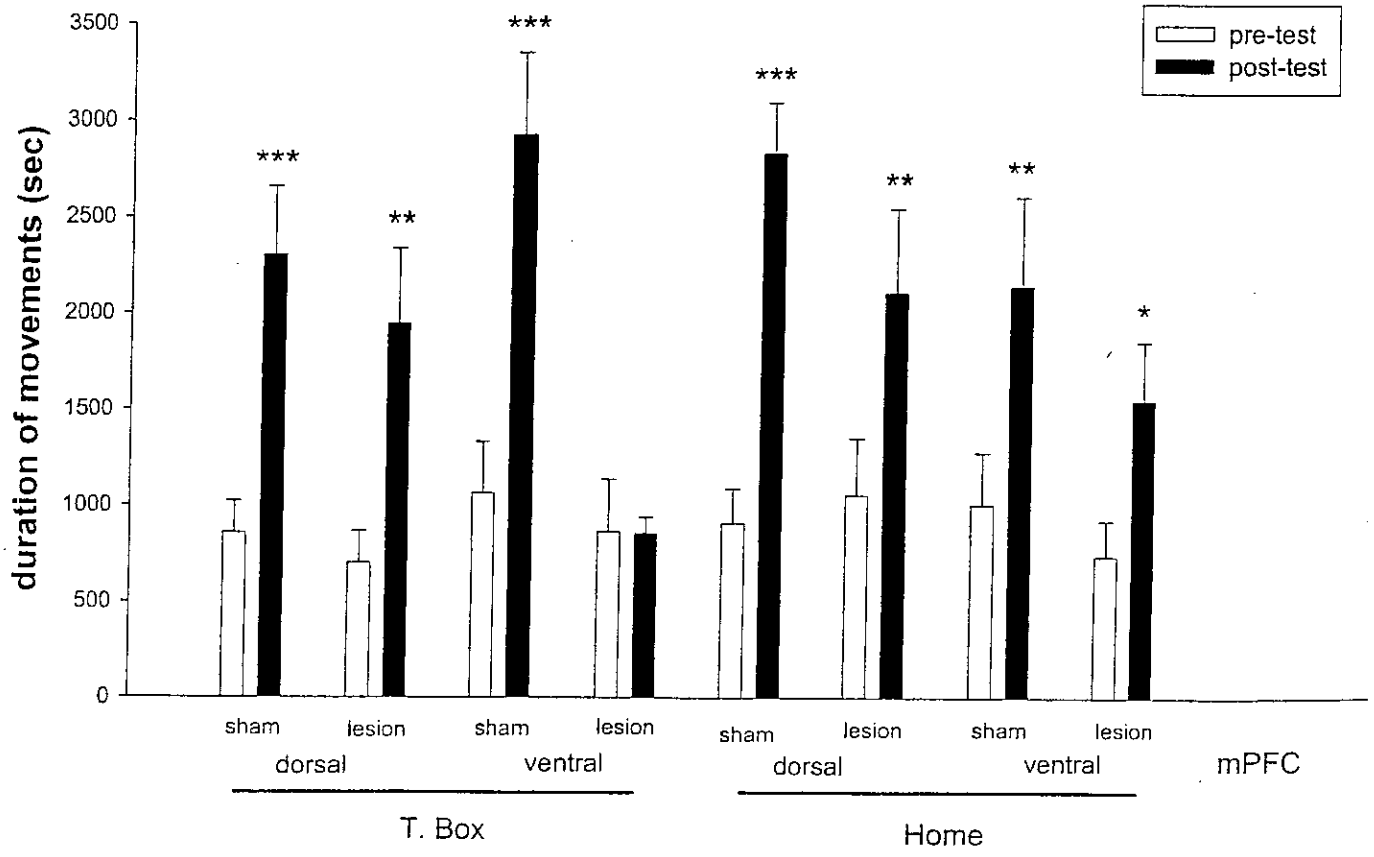


Fig. 8 The effects of ibotenic acid lesions in the dorsal and ventral subareas of the medial prefrontal cortex on the development of locomotor sensitization to d-amphetamine repeatedly administered in the test-box (T. box) and homecage (Home). Locomotor activities as measured by the number of counts (*top*) and the accumulated duration (*bottom*) of the detected movements on the pre- and post-test sessions for these two groups. Data are presented as means ±1 s.e.m. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; significant difference between pre-test and post-test on the indicated group.